THE DETERMINATION OF AMINO-COMPOUNDS OCCURRING AS IMPURITIES IN PHARMACEUTICAL CHEMICALS

PART III.

ARSANILIC ACID IN SODIUM *p*-GLYCOLLYL-AMINOPHENYLARSONATE AND IN CARBARSONE; SULPHATHIAZOLE IN SUCCINYLSULPHATHIAZOLE

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IN connection with the manufacture of sodium *p*-glycollyl-aminophenylarsonate (known by the trade name glycarsamide), carbarsone B.P., and succinylsulphathiazole. B.P., methods were required for the determination of the free amino-compounds. The British Pharmacopœia includes a limit test for sulphathiazole in succinylsulphathiazole which is based upon diazotisation and coupling with N-naphthyl-ethylenediamine in acidified aqueous alcohol. Carbarsone and glycarsamide, unlike acetarsol and tryparsamide, are soluble in this solvent hence there was the possibility of applying this method to them also. Consideration was also given to the use of *p*-dimethylaminobenzaldehyde which has been used for the determination of various compounds containing primary aromatic amino-groups[1,2,3,4].

DIAZOTISATION AND COUPLING METHOD

It was found that optimum conditions are not used in the B.P. limit test on succinylsulphathiazole and hence these were determined in the usual way and included in particular the use of a higher acid concentration. A further modification was the substitution of sulphamic acid for urea for removing excess of nitrous acid. Identical results were obtained at 5°C. and at room temperature hence the latter was used for convenience. Under the conditions adopted no hydrolysis of succinylsulphathiazole or carbarsone was detectable; some degree of hydrolysis of glycarsamide was expected in view of that reported for acetarsol[5] and actually was equivalent to 0·02 per cent. of amino-compound under the test conditions. Although decomposition of carbarsone, which is a derivative of phenylurea, by nitrous acid might have been expected, none was found. Calibration curves (extinction × concentration) for both arsanilic acid and sulphathiazole were almost linear.

To a mixture of 25 ml. of alcohol (96 per cent.), 12·5 ml. of N hydrochloric acid and 7 ml. of water, cooled to room temperature, add 0·02 g. of finely powdered sample and shake until dissolved. Add 1 ml. of 0·25 per cent. sodium nitrite solution, mix and set aside for 3 minutes. Add 2·5 ml. of 4 per cent. sulphamic acid solution, mix, set aside for 4 minutes, add 1 ml. of 0·4 per cent. solution of N-naphthyl-ethylenediamine hydrochloride, mix and dilute to 50 ml. Carry out a determination omitting the sample. Determine the extinction of each using

Ilford 605 filter, and read the amount of amino-compound from a calibration curve.

p-Dimethylaminobenzaldehyde Method

Methods for the determination of sulphonamides with *p*-dimethylaminobenzaldehyde have been described by Werner[2] and by Morris[3] and have the advantages of speed and simplicity. Optimum conditions were determined for the tests under consideration and, under these conditions, no hydrolysis occurred. Calibration curves again were almost linear.

Reagents. 1. p-*Dimethylaminobenzaldehyde Solution.* 2·5 per cent. solution of purified[6] *p*-dimethylaminobenzaldehyde in alcohol (95 per cent.).

2. *Citrate Buffer.* 0·75 M disodium hydrogen citrate solution. (39·4 g. of citric acid dissolved in 188 ml. of 2 N sodium hydroxide and the solution diluted with water to 250 ml.)

To a mixture of 9 ml. of N hydrochloric acid, 4 ml. of buffer, 17 ml. of water and 20 ml. of *p*-dimethylaminobenzaldehyde solution, cooled to room temperature, add 0·02 g. of finely powdered sample, shake until dissolved and, after 5 minutes, dilute to 50 ml. with water. Carry out a blank determination omitting the sample. Determine the extinction of each using Ilford 601 filter, and read the amount of amino-compound from a calibration curve.

Comparison of Methods

Table I shows substantial agreement between results obtained on all three substances by the two methods.

TABLE I

Comparison of methods

Compound	Sample	Amino-compound per cent.	
		Diazotisation and Coupling	*p*-Dimethylaminobenzaldehyde
Succinylsulphathiazole	1	0·23	0·21
	2	0·48	0·47
	3	0·36	0·36
	4	0·30	0·29
Carbarsone...	1	0·48	0·50
	2	0·77	0·81
	3	0·62	0·64
	4	0·74	0·74
Glycarsamide	1	0·16	0·14
	2	0·22	0·21
	3	0·29	0·31
	4	0·27	0·29

The *p*-dimethylaminobenzaldehyde method is simpler and more rapid, but photo-electric matching is necessary because the colour is yellow and the reagent blank relatively large. In the diazotisation and coupling method the blank is almost negligible and the purple colour is suitable for visual comparison. Neither method was found suitable without modification for the determination of sulphathiazole in phthalylsulphathiazole

owing to the exceedingly low solubility of the latter and a rather high rate of hydrolysis.

Proposed Limit Tests

Limit tests for free amino-compound in carbarsone and glycarsamide with limits of 1 per cent. and 0·5 per cent. respectively may be based on the diazotisation and coupling procedure. The same test, which differs from the official test in incorporating optimum conditions is applicable also to succinylsulphathiazole. Dissolve 0·02 g. of substance in a mixture of 25 ml. of alcohol (96 per cent.), 12·5 ml. of N hydrochloric acid and 7 ml. of water, previously cooled to room temperature. Add 1 ml. of 0·25 per cent. sodium nitrite solution, mix, and set aside for 3 minutes. Add 2·5 ml. of 4 per cent. sulphamic acid solution, mix, set aside for 4 minutes, add 1 ml. of 0·4 per cent. solution of N-naphthylethylenediamine hydrochloride, mix and dilute to 50 ml. The colour produced is not greater than that produced when the appropriate amount of arsanilic acid or sulphathiazole is treated similarly.

Summary

1. Two methods are described for the determination of free amino-compounds in carbarsone, glycarsamide and succinylsulphathiazole.

2. Limit tests, with a uniform method, are proposed.

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